Expert Opinion

Skin tolerability of transdermal patches

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Introduction: Transdermal patch systems are an effective method of administering active ingredients through the skin, with considerable advantages over other drug delivery routes, for example, maintenance of constant plasma drug levels and avoidance of first-pass metabolism. However, repeated epicutaneous application may be associated with local skin reactions.
Areas covered: This review addresses current issues regarding the effective/safe use of transdermal patch systems, and provides a critical analysis of the addition of 'skin-caring' ingredients to patch systems. Effective use of transdermal systems includes choosing an appropriate body area for application, maintaining regular skin care regimens before application and not replacing a patch in the same area (rotation) within 7 days. Another strategy, developed in an attempt to improve the tolerability of transdermal systems, is the addition of assumed 'skin-caring' ingredients (e.g., Aloe Vera) to patch systems. However, at present there is neither proof nor clinical evidence of any benefit. On the contrary, plant-derived ingredients might be associated with allergenic potential.
Expert opinion: Transdermal systems are generally well tolerated; physicians must adequately inform patients of the most effective ways to use these formulations for maximum therapeutic benefit, while minimising local adverse events. Skin-caring agents, including Aloe Vera, cannot be recommended until well-controlled clinical trials with standardised extracts are available.

Keywords: drug delivery, intolerance, safety and tolerability, transdermal patch systems

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1. Introduction

Transdermal patches are an effective method of drug administration, allowing an active ingredient to penetrate through the skin and become systemically bioavailable. Drugs administered by means of a transdermal patch reach the bloodstream by initially passing through the hydrophobic outer layer of the skin, the stratum corneum, before moving through the hydrophilic vital epidermal and dermal layers to enter the capillaries (**Figure 1**). In contrast to conventional topically acting drug patches, in which the effect of the active agent is limited to the area of application, a transdermal patch formulation is designed to facilitate systemic absorption and treatment. Agents considered best suited to transdermal delivery are those that are small molecules (< 500 Da) [1], pharmacologically potent and moderately lipophilic [2], and that bind minimally to skin proteins [3].

Transdermal formulations also have considerable pharmacokinetic advantages in terms of facilitating sustained release and absorption of the active substance over a long time period, providing constant plasma drug levels. This allows the maintenance of long-term therapeutic effects without troublesome symptoms returning. Adverse events occurring as a result of plasma peaks are also avoided and less frequent dosing is required, resulting in better compliance [4-6]. Moreover, administering a drug via a transdermal patch system also avoids first-pass

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Article highlights.

- Transdermal patch systems are an effective method of administering active ingredients through the skin; however, repeated epicutaneous application may be associated with local skin reactions.
- The key elements of local skin reactions include stripping effects, occlusive effects, heat-induced reactions and local intolerance.
- Strategies for the management of skin reactions include correct choice of patch application area on the body, careful removal of the patch post-treatment and the use of skin care products.
- Physicians need to communicate effectively to patients that correct patch handling, regular skin care and immediate treatment of skin irritations are the most efficient ways of minimising the effect of transdermal patch systems on skin function and limiting skin reactions.
- Aloe Vera is commonly used in cosmetic preparations as a 'skin-caring' ingredient; however, outcomes from the few available clinical trials are often contradictory, insufficiently documented and, hence, not clinically relevant.
- The recent development of incorporating Aloe Vera as a 'skin-caring' ingredient into transdermal patch systems in an attempt to mitigate local skin reactions is not supported by any robust clinical evidence; indeed, there is evidence that such plant-derived ingredients may be associated with allergenic potential.

This box summarises key points contained in the article.

metabolism in the liver, increasing bioavailability and exposing patients to fewer drug–drug interactions [7].

In addition to these pharmacological advantages, transdermal patches may also address practical issues associated with drug administration, thereby aiding compliance. Transdermal systems are a potential treatment option for patients who are unable to swallow pills, reduce pill burden in multimedicated individuals and may be advantageous because patients are not required to remember to take medication several times a day. Furthermore, a visual reminder that the medication has been taken can also be beneficial for many patients. Transdermal formulations have the potential to support caregivers in administering treatments to challenging patients, such as those with behavioural or psychiatric problems [8].

The first transdermal patch system was introduced in 1979 and contained scopolamine (hyoscine) for the prevention of nausea and vomiting associated with motion sickness [9,10]. This early system was composed of a thick layer of adhesive hydrogel containing the active agent, supported by a tissue layer [10]. Later, patches contained a 'reservoir' system with an outer backing layer, a raised reservoir containing the drug either dissolved into an alcohol solution or in solid or gel form, and a polymeric adhesive membrane to separate the reservoir from the skin and modulate delivery of the agent [3]. However, these patches bore the risk of dose dumping, with sometimes fatal consequences in the case of accidental damage. More recently, 'matrix' patches have become available, which combine the drug, a polymetric membrane, the adhesive and a backing layer into a single small, thin, flexible patch system (**Figure 2**). Development of the matrix system has encouraged the use of the transdermal patch, and more commercial systems are now available, containing agents such as buprenorphine, estradiol, ethinyl estradiol, fentanyl, nicotine, norelgestromin, norethindrone acetate, oxybutynin and testosterone. Indeed, transdermal medications are increasingly prescribed, particularly in the field of therapies for neurological and geriatric conditions [11].

Despite the advantages outlined above, gained with over 30 years of experience of using transdermal patch systems, this method of application is also associated with local adverse events, occurring in addition to those inherent to the drug being administered. Compared with earlier systems, the matrix system tends to be associated with improved tolerability owing to avoidance of the use of irritants (e.g., alcohol) as solvents for the active component [3]. However, local adverse events continue to be reported despite the advances in system design [12-14]. With more transdermal products being developed and prescribed, it is important to understand the common causes of skin reactions and the most effective way to minimise these reactions and manage adverse events.

A variety of regimens have been developed to optimise the benefits and minimise the risk associated with the available transdermal products so as to use them in the most appropriate way. The abdomen, buttock, upper outer arm and upper torso are generally suggested as suitable application sites for most patches. However, there are some product-specific recommendations: transdermal systems containing estradiol, for example, should not be placed on the breasts [15]. Generally, patches may be worn for periods ranging from 1 to 7 days. The growing number of medications available as transdermal formulations and their increased use highlight the necessity for clinicians to understand the principles of transdermal drug delivery, safe application techniques and how to advise patients properly on the use of these products [16].

2. Skin tolerability

Reliable fixation of the transdermal patch system to the skin is mandatory for optimal absorption of the medication, as close contact of the whole drug-containing area of the patch with the skin ensures controlled drug uptake [3,17].

2.1 Stripping effect

The adhesive strength of the patch leads to a stripping effect when the patch is removed from the skin, and is influenced by the area of skin in contact with the adhesive. Stripping results in the upper levels of the horny layer being removed, and the areas of skin that have been exposed to the patch systems may show signs of stress [10,17]. Repeated patch application, as well as their use in patients with sensitive skin, may cause irritation in the form of reddening, itching or scaling.

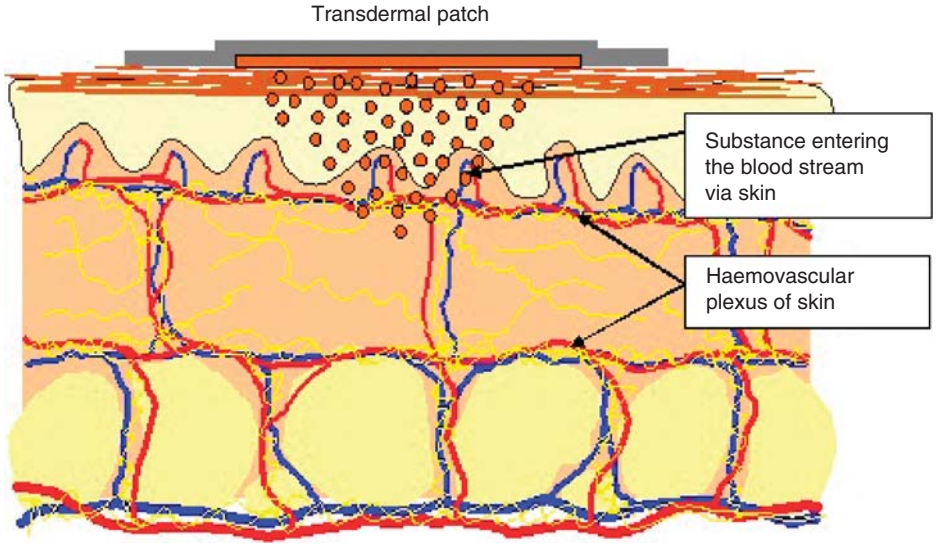

Figure 1. The active agent of a transdermal patch system enters the skin and passes through the stratum corneum and the lipophilic epidermal and dermal layers to enter the bloodstream.

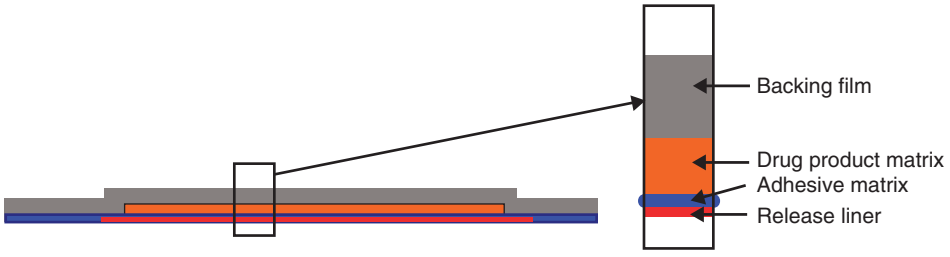

Figure 2. A cross-section of a typical matrix patch system.

With time, disturbed barrier function provokes an interaction of exogenic toxic substances in the skin, and this can lead to cumulative toxic irritant contact dermatitis, not just directly at the start of therapy, but months later.

2.2 Effects of occlusion

Application of the transdermal system to the stratum corneum produces an occlusive effect that facilitates and enhances transdermal drug absorption [1]. Indeed, occlusion leads to hyperhydration as increased water (up to 50%) enters the horny layer and increases the interaction of certain active ingredients with the skin. Active agents can enter the liquid, permeate the epidermis by the transcellular route (through corneocytes), the intracellular route (through intracellular lipids), or via both pathways and penetrate the dermis, all of which are necessary for a passive transdermal patch system to be effective [3]. The active agent is absorbed by the blood vessels of the superficial and deeper capillary plexus of the dermis and is then distributed throughout the body (**Figure 3**). However, by increasing hydration of the horny layer, occlusion reduces the effectiveness of the protective barrier of the epidermis owing to increased moisture pressure [2,3]. This may be associated with alterations in DNA synthesis in keratinocytes, skin surface pH, perspiration and in the function of dendritic cells, and may lead to the development of skin reactions [3,18]. These factors need to be considered when administering transdermal patch systems to patients in certain geographical locations, as skin reactions can be aggravated by humid, hot and dusty environments [3].

2.3 Heat-induced skin reactions

Some transdermal patch systems contain metals such as aluminium as part of the backing layer that serves to protect the patch from the environment. It has been reported that there is a possibility of experiencing burns when wearing these patches during an MRI scan [19]. These local heat-induced skin reactions can be clinically nonspecific so that differential diagnosis might be very difficult, especially for non-dermatologists. The metal in the back of a transdermal system may not be visible and, although many formulations contain a warning, not all products with metal components include this information in the labelling. Therefore, patients

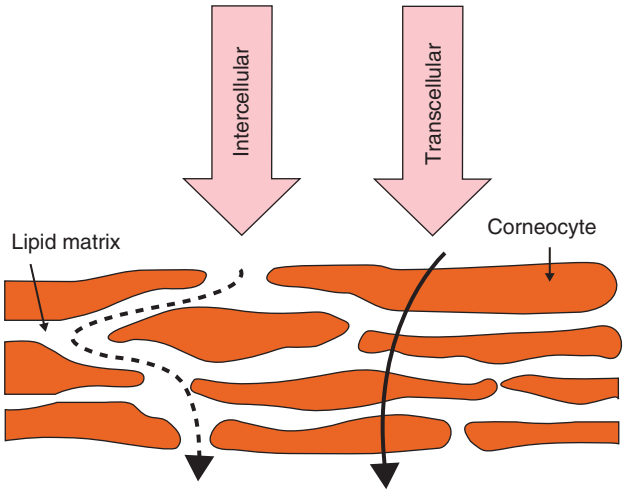

Figure 3. To enter the bloodstream from the skin, molecules must move across the intact horny layer, by using a transcellular or intercellular pathway, or both.

should discuss their transdermal patch and their reasons for using it with their doctor before an MRI scan [19].

2.4 Types of local intolerance reaction

Adverse effects experienced following application of a transdermal system may be caused by sensitisation to the adhesive, the ingredients of the transdermal system, extra skincare ingredients, or the active substance, and require professional testing to diagnose and treat the problem accurately (see Section 3) [3,20]. Generally, there are two basic localised reaction patterns: non-immunological and immunological intolerance [21]. Non-immunological intolerance reactions are divided into predictable (type A, toxic) and non-predictable (type B, pseudo-allergic) types [21].

2.5 Non-immunological intolerance

Non-immunological intolerance comprises mainly the following reaction types: toxic-irritative reactions, cumulative toxic reactions and delayed toxic reactions [21]. These effects are dependent on the concentration level and are usually limited to the site of contact with the noxious agent. Occasionally they occur after repeated contact, and the risk of these local skin reactions thus increases with long-term application. This is particularly relevant for products that are recommended to be applied for several days. The pathogenesis of predictable type A reactions can be explained by impairment of the barrier function of the horny layer due to occlusion, leading to an inflammatory response [21]. In certain cases, non-immunological reactions may be associated with superinfection, including the presence of secondary bacterial colonisation or other infection; then, depending on the source of infection, treatment should involve antiseptics, antibiotics or antiviral medications. Non-immunological skin reactions can usually be managed therapeutically and appropriate prophylaxis can help to reduce the risk of skin irritations [21].

Non-predictable type B reactions are either of known (idiosyncratic) or unknown (intolerance reaction) aetiology. Irritant contact dermatitis is a non-allergic, localised, inflammatory skin reaction to external chemical or physical agents, typically presenting with localised erythema and/or itching [22]. This reaction does not involve the central immune system and is the most commonly reported adverse reaction to many transdermal medications [12]. A recent review reported that signs and symptoms of irritant contact dermatitis usually arise from: damage to the corneocytes during patch removal; the blocking of sweat ducts of the follicles; removal of oil or lipids from the stratum corneum, leading to increased water loss; irritation caused by the active agent or other components of the patch; occlusion preventing water loss and trapping sweat; irritant effects of residual substances such as soap or lotions; and friction produced by differential shearing forces between immobile skin beneath the patch and the surrounding mobile skin [3]. All of these factors may cause damage to the stratum corneum and are likely to be exacerbated with continuous or repeated use, leading to inflammation and further damage [23,24]. The signs and symptoms tend to resolve after discontinuation of exposure to the transdermal patch system.

2.6 Immunological intolerance

Long-term use of transdermal patch systems may facilitate the penetration of potential allergens or haptenes that may result in sensitisation and immunological local reactions [21], which are grouped according to Gell and Coombs into pathoimmunological reaction types 1 – 4. These are based on sensitisation of the immune system and show typical clinical patterns. Allergic contact dermatitis is rare and usually presents with erythema, oedema and discharging vesicles of varying severity [25]. As this type 4 response is T-cell mediated, allergic contact dermatitis will not usually manifest on the first patch application unless a patient is already sensitised to a component of the treatment, or the concentration of the allergen or the area of application is sufficiently high. Sensitisation may develop only after weeks or months of treatment, but each subsequent patch application will elicit a skin response [25]. Conversely, type 1 reactions develop rapidly (within seconds to minutes) and are communicated through specific IgE mechanisms involving immune cells such as mast cells and basophils [26]. Patients generally present with urticaria or anaphylaxis. Immunological intolerance is rare and requires expert diagnosis, professional skin testing and treatment. If an allergic reaction occurs, treatment with the transdermal patch should be discontinued and the potential allergen should be identified by skin testing [21].

2.7 Further reactions

In very rare cases, serious types of skin reaction may occur, including contact urticaria, photo-irritation, systemic contact dermatitis and Steven-Johnson syndrome [3]. In these cases,

transdermal treatment should be discontinued immediately and a dermatologist should be consulted.

3. Evaluating skin reactions

Assessment of morphology (lesion type and localisation), time course (acute or delayed onset) and persistency of skin reactions forms the basis of establishing a differential diagnosis of irritant or allergic contact dermatitis [3]. Patch testing, although often inconclusive unless each transdermal system component can be tested appropriately, can assist in the diagnosis of allergic contact dermatitis [20].

4. Strategies to avoid skin intolerability

The occurrence of occlusion, stripping effects and other skin reactions is inevitable when using a transdermal system. However, effective preventive methods exist to manage skin reactions with transdermal patches, and physicians should inform patients of the optimal way to use transdermal patch systems in order to gain maximal benefits from drug treatment while minimising the experience of adverse reactions (**Table 1**).

4.1 Choice of application areas

The initial approach that should be used to minimise adverse events associated with the use of a transdermal system – taking into account the recommendations of the product information – involves selecting an appropriate area of skin on which to place the patch. Scars, moles and other blemishes should be avoided, as should broken, burnt or damaged skin areas, or any area already showing signs or symptoms of existing skin intolerability [3]. Patients with sensitive skin should choose the least sensitive areas for application, and sweat-conditioning activities and exposure to direct sunlight should be avoided while the patient is using the patch. Transdermal patch application should be regularly rotated between body areas recommended in the product information that demonstrate the greatest tolerability, with no reapplication of the patch to the same area of skin within a period of at least 7 (preferably 14) days [3]. Regular rotation of the application site and changing the site to a separate lymph node catchment area may reduce immunological exposure and prevent hypersensitivity and the occurrence of adverse effects [22,23,26,27]. It should be noted that different sites on the body may also show varying tolerance to irritant contact agents [28]. Hence, if a patient develops an adverse reaction to a patch, the most effective method for treating the symptoms may be to move the patch to a different skin location, according to the manufacturer's guidelines [3].

4.2 Removal of patch

Following the treatment period with a particular patch, patients should carefully remove the system to minimise damage to the stratum corneum [3]. The patch should be removed in a careful manner by mobilising one patch corner and moving this slowly and horizontally across the skin surface at a flat angle. This is particularly important in elderly patients who have more fragile skin [3]. As frequent patch removal may be associated with cumulative irritation resulting from stripping effects, patients may be advised to prolong the application period (up to the maximum time period according to the manufacturer's guidelines), thus reducing the number of patch removals.

4.3 Use of skin care products

A regular skin care regime using water-containing, lipid-rich, emulsifier-poor, perfume-free skin care creams (as used for atopic dermatitis) should be implemented. These products should be applied regularly to all potential patch application areas twice daily independently of an established skin reaction, but not immediately before a transdermal system is applied. Indeed, when preparing the skin for use of a transdermal system, any powder, oil, or moisture should be removed by gentle washing and drying [3]. Alcohols, soaps and detergents should be avoided as they may promote irritant or allergic skin reactions [20]. Any excess hair should be trimmed to a suitable length, but shaving should be avoided as it may aggravate the skin. Moisturisers and lotions may be used to relieve some of the symptoms of skin reactions, including dry skin and scaling, and encourage healthier skin [3]. This may also include use of antiseptic agents to minimise the risk of infection. However, the use of moisturising agents should be closely monitored because some products have been shown to worsen skin reactions [29]. Antihistamines or topically applied polidocanol-containing lotions may relieve itching, although possible adverse effects of extra treatments should be considered [3]. Topically administered corticosteroids or calcineurin inhibitors may be effective at reducing skin inflammation or irritation in some cases [3].

4.4 'Skin-caring' ingredients in transdermal patches

A further, recent approach to improve skin tolerability is the inclusion of 'skin-caring' ingredients such as Aloe Vera within the transdermal patch system. Aloe Vera (*Aloe barbadensis* Miller) is widely used in western society in the cosmetic industry [30] and, on this basis, transdermal products have recently been introduced on the market that contain a lipophilic Aloe Vera extract. This includes preparations containing buprenorphine with Aloe Vera for the treatment of chronic pain (e.g., in Germany, Buprenorphin-ratiopharm®; Buprenorphin AWD® Matrix, AWD.pharma GmbH & Co. KG, Radebeul), and vitamin B1 administered with Aloe Vera as an insect repellent (e.g., Don't Bite Me!® patch, Pearland, USA) [31,32]. From a dermatological point of view, the addition of Aloe Vera, the only 'skin-caring' ingredient included in transdermal patch systems at present, must be evaluated critically.

4.4.1 *Aloe Vera*

There are three distinct portions of the Aloe Vera plant: the rind, consisting of outer rinds, tips, bases and thorns; mucilaginous tissue in the centre of the leaves, which contains

Table 1. Management of skin reactions associated with transdermal medications [3,17,20-22,26].

Preparation of skin for use of a transdermal system	Follow a regular skin care regime using water-containing lipid-rich products
	Avoid scars, moles and other blemishes
	Avoid broken, burnt or damaged skin
	Patients with sensitive skin should choose the least sensitive areas
	Remove powder, oil and moisture before applying a patch
	Remove any excess hair by trimming rather than shaving
Good practice when using a transdermal system	Avoid sweat-conditioning activities
	Rotate the patch regularly
	Do not reapply a patch to the same area within a period of at least 7 days
	Change sites in the event of an adverse reaction (according to the manufacturer's instructions)
	Remove carefully to minimise damage to the stratum corneum
	Prolong application period to minimise number of patch removals (according to manufacturer's instructions)
	Avoid patches with sensitising ingredients
	Discuss the transdermal patch system with healthcare professionals before an MRI scan
Treatment options when skin reactions are experienced	Moisturisers and lotions to relieve symptoms of dry skin
	Aseptic agents to minimise infection risk
	Antihistamines to relieve itch
	Corticosteroids or calcineurin inhibitors to reduce contact dermatitis
	Antibiotics or antiviral agents to treat superinfection
	Avoidance of sensitising agents

the internal gel matrix or the 'fillet'; and the peripheral bundle sheath cells that produce the latex or sap. Aloe Vera contains multiple constituents with potential biological and toxicological activities, including glycoproteins, vitamins, enzymes, anthraquinones, minerals, saccharides, lignin, saponins, salicylic acids and amino acids [33]. However, the active components have not yet been conclusively identified [34].

Aloe Vera gel is a rich source of polysaccharides, most of which are β-(1,4)-linked, polydispersed, highly acetylated mannans, such as acemannan [35]. These polysaccharides have different properties depending on their size and the ratio of glucose to mannose [36], and are also affected by pH, certain enzymes and high temperatures [37]. Aloe Vera gel contains three malic acid acylated carbohydrates: veracylglucans A, B and C, which are hypothesised to possess anti-inflammatory effects. Veracylglucans A and B show antiproliferative effects, whereas veracylglucan C enhances cell proliferation [38]. Galactose and galactouronic acid polymers are also frequently found in gel extracts [39]. At least six enzymes are also reported to be present in Aloe Vera gel, including bradykinase, cellulase, carboxypeptidase, catalase, amylase and an oxidase [38].

The main constituents of Aloe Vera latex include phototoxic anthraquinones such as aloins A and B, aloe-emodin, barbaloin and isobarbaloin [40]. It should be noted that the anthraquinones are present in the latex portion of the leaf and are thus removed in the preparation of the gel. Several other C-glycosylchromones and anthrones have been isolated from Aloe Vera, including resins, aloesin, aloesone and chromone derivatives [40-45]. Other potentially active components such as lipids, amino acids, enzymes and sterols have also been identified in the latex [46].

A comparison between the constituents of the gel and the latex shows that, depending on the extract taken from the leaf, there is considerable variability in the components of Aloe Vera products that are commercially available. Other causes of variation in the constituents found in the leaves include the geographical region in which the plant was grown, season of growth/cultivation, climate, age and the part of the plant from which the leaves were obtained [47].

The components of the final product also depend on the processing method used. Obtaining products with active ingredients that can be used in preparations for human use requires processing the plant parts. The production process for extracting the ingredients from the Aloe Vera plant generally begins with pressing the pulp from the leaves. This is then followed by various filtration and stabilisation steps [48]. The resulting solution is mixed with other agents to produce a pharmaceutical, cosmetic or food product [49]. Owing to improper processing, Aloe Vera products often contain very few, if any, of the active ingredients that are likely to be responsible for the biological effects. Other methods may include extraction procedures using aqueous or ethanol-containing solvents. Indeed, soybean oil may be used to extract more lipophilic components. However, there is limited information within the literature detailing processing procedures and it is difficult to assess whether methods are consistent between studies.

Some small cosmetic studies to assess the effect of Aloe Vera on the skin have been performed [50]. One study evaluated the effects of cosmetic formulations containing

different concentrations of freeze-dried Aloe Vera extract on skin hydration in female volunteers [51]. After both a single application and a 2-week period of use, formulations supplemented with Aloe Vera extract increased the water content of the stratum corneum compared with the control preparation. These results indicated that freeze-dried Aloe Vera may improve skin hydration, although there are limited other studies available for comparison [51]. Furthermore, as discussed earlier, hyperhydration of the skin is an effect of occlusion that may lead to adverse skin reactions.

There is some evidence to indicate that Aloe Vera may cause cell proliferation, with potential benefits in wound healing [34,52]. Wound healing is considered to consist of the overlapping events of inflammation, new tissue formation and matrix remodelling [53], and several preclinical studies have investigated the effects of Aloe Vera in these processes. However, results are conflicting, reflecting the use of different, poorly characterised commercial products rather than native plant components, making conclusions difficult [34]. Findings from animal studies have also been inconsistent, with some studies suggesting benefits of Aloe Vera in wound healing [54,55], whereas others have reported detrimental effects [56]. The differences in these findings were postulated to be due to some studies utilising an Aloe Vera plant-derived gel, whereas others used a commercial Aloe Vera gel product [34]. This demonstrates the difficulty in interpreting the effect of Aloe Vera on the skin as long as the products utilised are not consistent or standardised.

Most clinical studies regarding Aloe Vera extracts have generally focused on wound healing properties in a variety of conditions including dermabrasion and psoriasis, and following gynaecological surgery or radiation therapy [57-62]. These studies were of variable study design quality and produced conflicting results, highlighting the fact that there are no large, well-controlled clinical trials conforming to GCP-ICH guidelines that have rigorously assessed the beneficial or detrimental effects of Aloe Vera on the skin. As a result, there are limited evidence-based data available. Therefore, the use of Aloe Vera is not recommended at present in any clinical guidelines. The trials that have been published tend to have methodological flaws and are generally performed by the same research groups, and independent replication/validation is lacking [63]. It should be noted that the use of Aloe Vera in cosmetic products is not clinical evidence of a medically beneficial effect, and well-controlled clinical trials are required before Aloe Vera can be recommended as a suitable ingredient for use in transdermal systems.

5. Conclusion

This review summarises current evidence supporting the effective use of transdermal patch systems. Despite the potential for local skin reactions, transdermal patch systems are generally well tolerated. However, it is important that physicians inform patients adequately regarding the most effective ways to use transdermal patch formulations in order to provide maximum therapeutic benefit while also minimising local adverse events. The recent development of incorporating skin-caring ingredients, such as Aloe Vera (commonly used in the cosmetics industry), into transdermal patch systems in an attempt to mitigate local skin reactions is not supported by any robust clinical evidence. Indeed, there is evidence that such plant-derived ingredients may be associated with allergenic potential. The use of such skin-caring ingredients as pharmaceutical agents cannot be recommended until large, well-controlled clinical trials with standardised extracts have been conducted.

6. Expert opinion

Most skin reactions observed with current transdermal formulations are mild in severity, transient in nature and should resolve spontaneously once the patch has been relocated to an alternative site [3]. Signs and symptoms of skin reactions are most likely to result from inflammatory responses to the stripping effect caused by patch removal, which causes minimal pain and is unlikely to be of any medical concern [3]. The potential advantages of transdermal medications over other methods of drug delivery usually outweigh skin tolerance issues [3], particularly if skin reactions are correctly treated and managed. However, many patients discontinue treatment when experiencing adverse events without full consideration of the available options for reducing the occurrence of such effects. Physicians need to communicate effectively to patients that correct patch handling, regular skin care and immediate treatment of irritations are the most efficient ways of minimising the effect of transdermal patch systems on skin function and of limiting skin reactions [12,17], and that discontinuation of the therapy is rarely necessary. As more transdermal products are developed and prescribed in increasingly diverse therapeutic areas, the requirement for healthcare professionals to understand the possible pathogenesis of skin reactions and to understand clearly the most effective methods for skin reaction prophylaxis and treatment is very relevant, and further investigation into this topic is warranted [3].

Aloe Vera gel is commonly used in cosmetic preparations. Owing to its widespread use within this setting, Aloe Vera has a very positive image. It should be noted that this reputation cannot be transferred to pharmaceutical products, especially transdermal systems, containing Aloe Vera. Furthermore, claims from the cosmetic industry that Aloe Vera has skin-caring properties are not transferable to support its pharmaceutical use, and it is not possible to evaluate these in controlled clinical trials because there is no clear definition of what these properties entail. Outcomes from the few available therapeutic trials are often contradictory, insufficiently documented and, hence, not clinically relevant.

With a lack of published scientifically validated support, and the fact that there may be risks involved in using extra ingredients that have not been adequately evaluated by evidence-based medicine, the use of Aloe Vera in transdermal formulations cannot be recommended at present.

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